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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 249/08, 233/64, 231/12, C07F 9/6518, 9/6503, A61K 31/41, 31/675

A1

(11) International Publication Number: **WO 98/55463**

(43) International Publication Date: 10 December 1998 (10.12.98)

(21) International Application Number: PCT/EP98/03496

(22) International Filing Date: 4 June 1998 (04.06.98)

(30) Priority Data:
MI97A001328 5 June 1997 (05.06.97) IT

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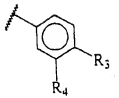
(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DIPHENYL-TRIAZOLE DERIVATIVES AND THEIR USE AS ANTI-GESTATIVE, IMMUNO-SUPPRESSANT AND ANTI-TUMORAL AGENTS

(I)



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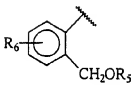

(III)

(57) Abstract

Compounds of formula (I), wherein X and Y are independently carbon or nitrogen (but no both simultaneously carbon), R_1 is a group (II) and R_2 is a group (III), R_5 being a carbonate, carbamate or phosphate residue, are useful as anti-gestative, immuno-suppressant and anti-tumour agents.

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DIPHENYL-TRIAZOLE DERIVATIVES AND THEIR USE AS ANTI-GESTATIVE, IMMUNO-SUPPRESSANT AND ANTI-TUMORAL AGENTS

OBJECT OF THE PRESENT INVENTION

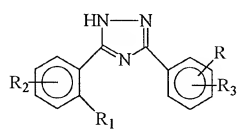
Objects of the present invention are nitrogen heterocyclic aromatic derivatives and their use as anti-gestative, immunosuppressant and anti-tumoral agents.

Object of the present invention is also a procedure for the preparation of nitrogen heterocyclic aromatic derivatives.

Object of the present invention is again a pharmaceutical composition which contains, as active principle, at least one heterocyclic aromatic according to the present invention.

STATUS OF THE TECHNIQUE

Chemical classes of compounds endowed with anti-gestative activity are known, more specifically BE 866,728 reports a class of 3, 5-diphenyl-1H-1, 2, 4 triazoles of the



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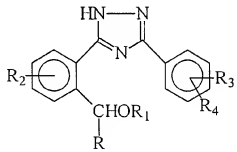
following general formula:

where R_1 is an alkyl group C_1-C_4 .

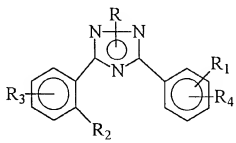
EP11129 reports 1, 2, 4 triazoles derivatives of the following general structure:



where R is hydrogen or methyl and R_1 is hydrogen or an alkyl group C_1-C_4 , or R_1 and R_2 together form an additional bond between the carbon and oxygen atoms.

BE 879,732 reports a class of compounds showing the following general structure:

where, among the other possible substitutions, R is an



hydrogen or a R_5-CO group where R_5 is chosen among alkyl C_1-C_4, alkenyl C_2-C_4 and alkinyl C_2-C_4 , whereas R_2 is a -$CH(R_7)OR_8$ where R_7 is an hydrogen or methyl and R_8 is like R_5-CO.

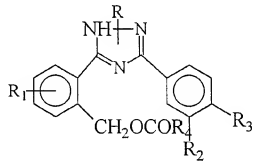
In the above mentioned disclosed documents, the pharmacological data show how these compounds display a high anti-gestative activity after repeated parenteral administrations (daily up to 5 consecutive days). The literature describes the compound 3-(2-ethyl-phenyl)-5-(3-methoxy-phenyl)-1H-1,2,4-triazole, also identified by the code DL 111-IT (Reviews on Drug Metabolism & Drug Interactions, Vol. IV, N. 2&3, 1982, A. Assandri, A: Omodei-Sale', G. Galliani).

The mentioned DL 111-IT, reported in BE 879,732, did show an interesting anti-gestative activity in all the investigated animal species including the mouse, the rat, the hamster, the dog and monkeys. DL 111-IT has been proposed as anti-gestative agent for human use.

These previously disclosed anti-gestative compounds, including the compound DL 111-IT, when tested according to a protocol which foresee a single dose parenteral treatment, displayed their activity at doses much higher than those required by multiple dose regimens.

EP0080053 describes 3, 5 diphenyl-1H-1, 2, 4 triazole derivatives that, as compared to the previously reported derivatives, have been structurally modified in order to obtain a high anti-gestative activity after a single-dose parenteral administration by subcutaneous and intramuscular route.

The compounds described in EP0080053 have the following general structure:



where, R is chosen between hydrogen and R_5CO-, where R_5 is a saturated or non-saturated aliphatic C_1-C_{20} hydrocarbon chain, R_1, R_2 and R_3 are chosen among hydrogen and short-chain alkyl or alkoxyl, or R_1 and R_2 together form a methylendioxy group, R_4 is a saturated or non-saturated aliphatic C_1-C_{20} hydrocarbon group.

The above mentioned derivatives, when given by single dose to rodents, displayed a high anti-gestative activity. This activity was however shown to be highly

species-specific. Actually, while in rodents it was very high, in the higher mammal species, like the dog, the anti-gestative activity markedly decreased, due to a too slow hydrolysis rate of the administered products that undergo metabolism before the active principle become bioavailable.

OBJECTIVES OF THE INVENTION

Objective of the present invention is to make available nitrogen heterocyclic aromatic derivatives endowed with high anti-gestative activity when administered as single dose to different animal species including higher mammals and man.

Objective of the present invention is also to make available nitrogen heterocyclic aromatic derivatives endowed with high immuno-suppressant activity.

Again, objective of the present invention is to make available nitrogen heterocyclic aromatic derivatives endowed with non species-specific anti-gestative, immuno-suppressant and anti-tumour activity.

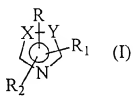
Again, objective of the present invention is to make available nitrogen heterocyclic aromatic derivatives endowed with a sustained duration of action, thus able to display the desired activity by a single-dose treatment

(anti-gestative activity) or by multiple dose treatments with wide inter-administration time intervals (immuno-suppressant and anti-tumour activities).

Objective of the present invention is also to make available a pharmaceutical formulations, containing at least one nitrogen heterocyclic aromatic derivative as active principle, easy to be administered, well tolerated and able to allow a high therapeutic index.

DESCRIPTION OF THE INVENTION

These and other objectives with further advantages which are clarified in the description below, are obtained by the nitrogen heterocyclic aromatic derivatives having the following general formula:



(I)

where:

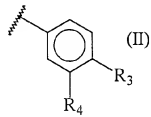
-when X=Y, X, Y=N;

-when X=Y, X, Y=N, C, CH;

-R is chosen between hydrogen, $-COR_8$ where R_8 is a saturated or non-saturated C_1-C_{10} aliphatic hydrocarbon,

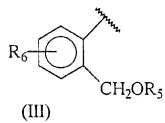
or R represents any other group able to form a bond with a nitrogen atom;

- R_1 has the following general formula:



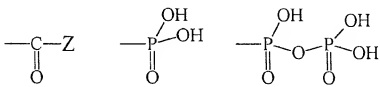
where R_3 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, R_4 is chosen among hydrogen, alkyl or alkoxyl C_1-C_{10}, or R_3 and R_4 together form a methylendioxy group;

- R_2 has the following general structure:



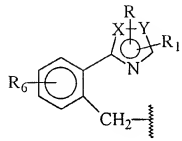
(III)

where R_5 is chosen among:



where $Z=OR_7$ with R_7 is chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic

hydrocarbon, or is chosen according to the following formula:



(XII)

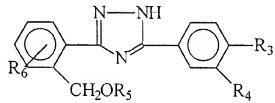
where R, R_1, X and Y are defined as above and R_6 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, or Z is chosen equal to NHR_8 where R_8 is a linear or branched C_1-C_{20} alkyl chain. Mentioned R_1 and R_2 are never located on two adjacent atoms of the heterocyclic aromatic ring.

According to the present invention, the term saturated or non-saturated aliphatic hydrocarbon means a linear or branched alkyl, alkenyl or alkinyl chain which contains one or more double or triple bonds. Always according to the present invention, the term alkyl or alkoxyl means a linear or branched alkyl or alkoxyl group.

Namely, the mentioned nitrogen heterocyclic aromatic derivative of formula (I) is a derivative of pyrazole, imidazole and 1H-1, 2, 4-triazole respectively:



According to the present invention, the mentioned derivative of formula (I) is a triazole derivative having the following general formula:



(IV)

where X=Y=N, while the other substituents are defined as for the derivative of formula (I).

Of particular interest are those derivatives of formula (IV) where R_6 is hydrogen, R_4 is $-OCH_3$ or $-OCH_2CH_3$, R_3 is hydrogen, R_5 is chosen equal to COZ where $Z=OR_7$ with R_7 as a saturated linear aliphatic C_1-C_{12} hydrocarbon.

Always according to the present invention, of particular interest were those derivatives having the following formulas:

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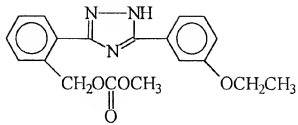
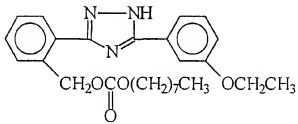
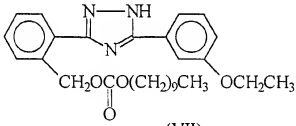


(V)



(VI)



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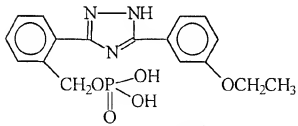
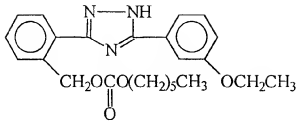
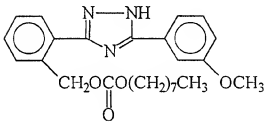


(VIII)



(XVI)



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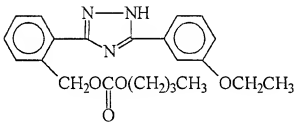
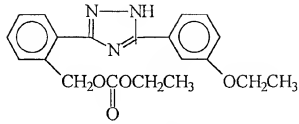
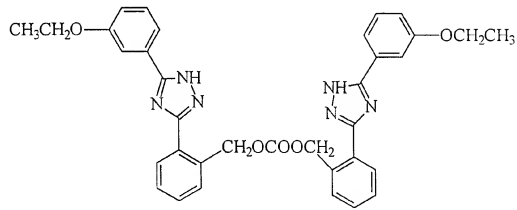


(XIV)

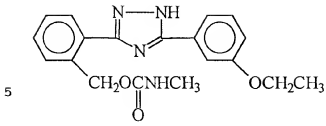


(XV)

In addition according to the present invention, of particular interest were the two derivatives having the following formulas:



(XVII)



(XVIII)

As reported in the literature, see Potts K.T , J: Chem. Soc. 3451, (1954) and Potts K.T., Chem. Rew. 61, 99 (1961), Kubota and Uda, Chem. Pharm. Bull. 23(5), 955 (1975), due to the high mobility of the hydrogen atoms of 1, 2, 4-triazoles, compounds of formula (I) of the present invention where X=Y=N, are to be regarded as a mixture of two tautomeric forms, i.e. those in which the hydrogen atom is located on one or the other of the two adjacent nitrogen atoms of the triazole ring. Depending on the nature of the substitutes at the 3 and 5 positions, a form may predominate on the other one. Consequently, both mentioned tautomeric forms must be considered as part of the present invention. It is known that tautomeric forms rapidly exchange in between and consequently behave as a dynamic equilibrium.

Anyway, throughout the whole description and claims relative to the present invention, 3, 5 diphenyl-1H-1, 2,

4-triazoles according to the present invention, will be numbered as reported above for derivative (V).

The derivatives of the present invention are provided of anti-gestation, immuno-suppressive and anti-tumour activities Particularly, the anti-gestative activity is displayed by a single dose regime and it does not requires a prolonged treatment. Furthermore, these derivatives show high therapeutic indexes, since a remarkable efficacy is achieved at doses much lower than the toxic ones able to induce undesirable adverse events. The compounds of the present invention of formula (I), when administered as a single parenteral injection displayed more than one pharmacological activity, namely:

(a) they have proven to be highly effective in terminating pregnancy in rodent and non-rodent animal species;

(b) they have proven to be highly effective in reducing both the humoural and cellular immunological response in animal models predictive for the pharmacological activity in humans

(c) in addition, the compounds of the present invention while lacking of effectiveness in different tumour models, showed a specific marked activity on an model of human chorio-carcinoma transplanted in nude mice.

The different pharmacological activities displayed by the derivatives object of the present invention, are attributable to a common mechanism of action.

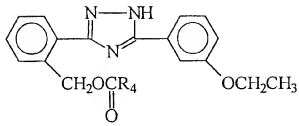
The reference model which explains this multiple pharmacological action is an atypical rapidly proliferating cell system, the placenta.

As reported by Aitken, Beaconsfield and Ginsher in their comprehensive review "Origin and formation of the placenta", this system, during its early stage of development, has strong similarities to tumour (1). Among these in particular, the placenta is tolerated by the maternal host due to an alteration of the immune responsiveness with no inflammatory response to blastocyst and/or trophoblast invasion.

Biochemical studies on placental tissue, during the early post-implantation period, demonstrated that the contra-gestational activity of 3,5 diaryl-1H-1,2,4-triazoles occurs through a selective action on the decidual and trophoblastic cells. Reasonably, this selective anti-proliferative action can also account for the activity of 3,5 diaryl-1H-1,2,4-triazoles against a gestational tumour like chorio-carcinoma. Finally, the immuno-suppressant response, which closely relates to the contra-gestational potency of 3,5 diaryl-1H-1,2,4-

triazoles , may either be the early or the late response of the primary biochemical alterations.

The derivatives object of the present invention are characterised by the presence of an easily hydrolysed bond through non species-specific enzymatic reactions occurring on R_5 group ; this hydrolysis allows the release of the active principle that can display its *in vivo* action. The characteristic bond of R_5 group present in the derivatives object of the present invention, is different from the bonds described in the already disclosed derivatives, and it can be hydrolysed according to different mechanisms of reaction. Because of these properties , unlike the compounds already disclosed, the compounds objective of the present invention are also effective in higher mammal species, including humans. With the aim of evaluating whether inter-species difference could exist in the enzymatic reactions of the ester bond, compounds (XV), (XIV, VI) ad some known derivatives described in EP0080053 (compounds A ,B and C) have been tested *in vitro:*



where when R_4 is chosen as $-C_3H_7$ the compound is named A; where when R_4 is chosen as $-C_7H_{15}$ the compound is named B;

Where when R_4 is chosen as $-C_8H_{23}$ the compound is named C;

These compounds dissolved in an ethanol mother solution, when incubated in diluted (1:4 v/v, with saline, 0.9% NaCl) rat, dog and human serum at a 10^{-5} M concentration for 1 hour at 37°C underwent enzymatic hydrolysis. The hydrolysis rates, expressed as nMoles/hour of the active principle formed, i.e. 3-(2-hydroxymethyl-phenyl)-5-(3-ethoxyphenyl)-1H-1,2,4 triazole, corresponding to the compound described in EP0080053, were measured. The values obtained, reported in Table 1, show how, in the higher species considered, i.e. the dog and man, the known products A, B and C undergo hydrolysis very slowly whereas compounds (XIV), (XV) and (VI), are rapidly metabolised both by rat, dog and human serum.

TABLE 1 : *HYDROLYSIS RATE OF SELECTED 3-(3-ETHOXYPHENYL)-5-(2-ACYL-CARBOXYMETHYL-PHENYL)-1H-1,2,4 TRIAZOLES, COMPOUNDS (XV), (XIV) and (VI) AND SELECTED 3-(3-METHOXYPHENYL)-5-(2-ACYLOXYMETHYL-PHENYL)-1H-1,2,4 TRIAZOLES, COMPOUNDS (A), (B) AND (C)*

COMPOUND	Rate of Hydrolysis (nmoles/hour)		
	RAT	DOG	MAN
(XV)	≥ 120	≥ 120	≥ 120
A	≥ 120	16	12
(XIV)	≥ 120	≥ 120	≥ 120
B	≥ 120	3	2
(VI)	≥ 120	≥ 120	≥ 120
C	≥ 120	< 0.5	< 0.5

Since the metabolic attack (de-alkylation) of these structures, occurring in position meta with respect to the substituent R_1 of structure (II), gives rise to inactive or poorly active metabolites, a too slow hydrolysis of compounds A, B and C will lead to a marked reduction of the activity of these molecules in the higher species. On the contrary, as already mentioned, derivatives of the present invention of formula (I), can be usefully used in higher mammal species including the dog and man. The compounds of the present invention

actually represent a class of new non-hormonal, non-prostaglandin, like, post-coital, post-implantation anti-fertility agents particularly useful for terminating pregnancy in mammals following a single dose treatment at very low doses.

The pregnancy-terminating activity of the compounds of the present invention has been assessed by carrying out experiments in rats and dogs.

In particular, female Sprague Dawley rats weighing 200-230 g. were mated and the presence of sperm was detected, was considered day one of pregnancy.

Pregnancy was later confirmed at the time of autopsy by the presence of implantation sites in the uterus.

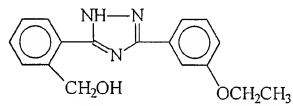
Test compounds dissolved in sesame oil containing 20% benzyl benzoate (or suspended if insoluble), were administered subcutaneously, in a single injection, on day 7 of gestation. The animals were then autopsied on day 16 of pregnancy and the uteri were examined for evidence of pregnancy (implantation sites, foetal resorption or live foetuses), haemorrhage, and evidence of abnormalities of the uterus, placenta or foetuses, *for reference see G. Galliani et al. Contraception, 23, 163-180 (198)..*

The compounds were tested at different doses in order to study the dose-activity relationship and their activity,

reported below in Table 2, has been expressed as ED_{50} values.

These values identify the dose levels which terminate pregnancy (absence of live foetuses) in 50% of the treated animals. For comparison purposes, the ED_{50} of some related triazoles previously disclosed (Belgian patents 866,728 and 879,732 and European patent application publication No. 11,129), are reported.

In particular compound D (active principle), has the following structural formula:



and it has been prepared as described in EP 11129, while compound E, prepared as described in BE 879732 and identified as DL111-IT, has the following formula:

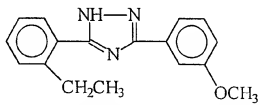


TABLE 2 : *PREGNANCY TERMINATION ACTIVITY IN S.D. RATS AFTER A SINGLE SUBCUTANEOUS INJECTION AT DAY 7 OF GESTATION*

Compound	ED_{50} mg/kg	ED_{50} μmoles/kg
(XV)	15	27.2
(XIV)	8	20.3
(XVI)	5	11.8
(VI)	2	4.4
D*	16	54.6
E**	35	125.4

*5-(2-Hydroxymethylphenyl)-3-(3-ethoxy-phenyl)-1H-1, 2, 4-triazole described in the European patent application Publication No. 11, 129

**5-(2-Ethylphenyl)-3-(3-methoxyphenyl)-1H-1, 2, 4-triazole, DL 111-IT, described in example 24 of Belgian patent 879, 732

The results obtained show how the compounds of formula (I) object of the present invention administered by a single parenteral injection are much more effective of the two compounds previously disclosed taken as reference.

Acute toxicity studies did show as the lethal doses of compounds (VI), LD_{50} > 500 mg/kg, are of three order of magnitude higher than those anti-gestative.

In another experiment carried out in Beagle bitches (0.9 - 4.5 y, 7 - 12.5 kg), compound (VI), i.e. 3-(2-decanoyl-oxymethylphenyl)-5-(3-ethoxy phenyl)-1H-1, 2, 4-triazole, when administered as a single intramuscular dose between the day of mating and the 25th day of gestation was found to be highly effective and very well tolerated.

The compound was given intramuscularly in one depot site of the thigh muscle of the right hind leg dissolved in sesame oil at the dose of 5 mg/kg (11.1 *µmoles/kg* , 40 mg/mL, 0.2 mL/kg). The anti-gestative effectiveness was ascertained by exploratory laparatomy examining uterine horns where the presence of live or dead foetuses was deduced from the dimension and appearance of each uterine swelling, for methodological reference *see G.Galliani et al.,J. Small Animal Practice, 25, 211-222 (1984).*

TABLE 3 : CONTRAGESTATIONAL EFFECT OF COMPOUND (VI), GIVEN AS SINGLE I.M. DOSES BETWEEN THE DAY OF MATING AND THE 14TH DAY OF GESTATION.

Administration (days of gestation)	**Dose** (*µmoles/kg*)	**No of bitches**	**Pregnancy arrest** (%)

15	5 (11.1)	5	80
20	5 (11.1)	5	100
25	5 (11.1)	5	100

The compounds of the present invention displayed significant immuno-suppressive activity on both humoral and cellular immunity when administered during the inductive phase of the immuno response, i.e. soon after antigen challenge. In experimental models of auto-immunity and skin transplantation they were able to reduce auto-antibody production as well as to prolong the skin graft survival.

The immuno-suppressant activity of the compounds of the present invention was assessed by carrying out experiments in mice.

In detail, the *Antibody Response to Sheep Red Blood Cells (SRBC) and to Lipo-polysaccharide (LPS)*, was studied in B6D2F1 mice injected intravenously 10^8 SRBC (day 0). Direct (IgM) and indirect (IgG) plaque forming cells (PFC) were evaluated in the spleen 4 and 10 days later, *Jerne et al. Science 140, 405 (1963) and Dresser and Wortis, Nature, 208, 859(1965)*.

Indirect PCF were developed with rabbit anti-serum to mouse gamma globulin.

B6D2F1 mice were immunised with 20 µg LPS intraperitoneally. Four days later, PCF were determined in the spleen by SRBC coated with LPS, *Moller, Nature, 207, 1166(1965)*.

TABLE 4 : *IgM ANTIBODY RESPONSE TO SRBC AND LPS AFTER SINGLE TREATMENT WITH COMPOUND (VI) COMPARED TO THAT OBTAINED AFTER MULTIPLE TREATMENT WITH THE REFERENCE COMPOUND E (see Mistrello et al., 1985)*

COMPOUND	ANTIGEN	DAY OF DOSING	DOSE (µmoles/Kg/day)	PCF/spleen $.10^{-3}$ (mean ± S.D.)
(VI)	SRBC	0	vehicle	124 + 18
	SRBC	0	8.60	12 + 3*
	LPS	0	vehicle	10 + 2
	LPS	0	8.60	3 + 1*
E	SRBC	0,1,2,3	vehicle	115 ± 20
	SRBC	0,1,2,3	17.92	7 ± 2*
	LPS	0,1,2,3	vehicle	11 ± 2

	LPS	0,1,2,3	17.92	4	±
			1*		

* p<0.01

TABLE 5 : *IgG ANTIBODY RESPONSE TO SRBC AFTER SINGLE TREATMENT WITH COMPOUND OF (VI) COMPARED TO THAT OBTAINED AFTER MULTIPLE TREATMENT WITH THE REFERENCE COMPOUND E (see Mistrello et al., 1985)*

COMPOUND	DAY OF DOSING	DOSE (μmoles/Kg/day)	PFC/SPLEEN.10^{-3} (mean + S.D.)
(VI)	0	vehicle	24 + 3
	0	2.15	3 + 3*
E	0 - 3	vehicle	26 + 4
	0 - 3	3.58	4 + 3*

Delayed Type hypersensitivity (DTH), was carried out in C57B1/6 mice administered subcutaneously 2 x 10^8 SRBC emulsified in complete Freund's adjuvant. Ten days later an eliciting dose of 10^8 SRBC was inoculated into a footpad. The DTH reaction was recorded 24 hours later by measuring the footpad swelling *(Kerckhaert et al, Cell Immunology, 29, 232,(1977)*.

TABLE 6 : *EFFECT ON DTH AFTER SINGLE TREATMENT WITH COMPOUND OF COMPOUND (VI) COMPARED TO THAT OBTAINED AFTER MULTIPLE TREATMENT WITH THE REFERENCE COMPOUND E (see Mistrello et al., 1985)*

COMPOUND	DAY OF DOSING	DOSE (µmoles/Kg/day)	FOOTPAD SWELLING UNITS* (Mean + S.D.)
(VI)	0	vehicle	11.4 + 3.7
	0	8.60	5.2 + 1.2**
E	0,1,2,3,4,5,6, 7,8	vehicle	10.1 + 3.3
	0,1,2,3,4,5,6, 7,8	17.92	4.1 + 1.4**

*1 unit = 0.1 mm, **p< 0.01

For the *Skin Grafting*, fitted pinch grafts of skin from C3H ($H\text{-}2^k$) donor mice were transplanted onto C57B1/6 ($H\text{-}2^b$) recipient mice (Mistrello et al,. 1984). Bandages were removed 7 days later and graft were scored daily by microscopy. Rejection was recorded when no viable epidermis remained. The median survival time (MST) of the

grafts, measured as days, was calculated according to Litchfield (1949).

TABLE 7 : *EFFECT ON SKIN GRAFT SURVIVAL TIME (MST) AFTER 1 WEEKLY TREATMENT WITH COMPOUND (VI) COMPARED TO THAT OBTAINED AFTER MULTIPLE TREATMENT WITH THE REFERENCE COMPOUND E (see Mistrello et al., 1985)*

COMPOUND	DAYS OF DOSING	DOSE (μmoles/Kg/day)	MST , days (mean + S.D.)
(VI)	-1, 7	vehicle	10.7 + 0.4
	-1, 7	17.20	15.1 + 0.6*
E	-1,1,3, 5, 7, 9,11	vehicle	11.0 + 0.4
	-1,1,3, 5, 7, 9,11	89.61	14.7 + 0.7*

* $p < 0.01$

Finally, the compounds of the present invention are endowed with a high and specific anti-tumour activity as demonstrated on an in vivo test against human chorio-carcinoma.

In particular compound of example 5 was highly effective in inhibiting the growth of a human chorio-carcinoma transplanted into nude mice. The potency of the tested compound was even higher than that displayed by methotrexate, the choice drug in the therapy of chorio-carcinoma.

Noteworthy, choriocarcinoma is a gestational tumor derived from trophoblastic cells, which, toghether with decidual cells, was suggested as the target site of the anti-proliferative action of 3, 5 diaryl-s-1,2,4 triazoles (Galliani et al. 1986).

For their use in suppressing the immunological response, in terminating pregnancy, and in treating chorio-carcinoma, the compounds of the present invention are embodied into topical, transdermal and injectable dosage forms to be administered epicutaneously or parenterally, i.e. subcutaneously, intramuscularly or intravenously. Such composition are formulated using proper transdermal delivery systems (epicutaneous dosing), aqueous (intravenous dosing) or non-aqueous vehicles (epicutaneous, subcutaneous and intramuscular dosing).

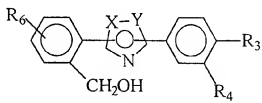
As examples of such systems/vehicles, the following can be considered for epicutaneous, subcutaneous and intramuscular dosing : oils of vegetable origin or fatty

esters such as sesame oil, corn oil, peanut oil, cotton seed oil, and ethyl oleate can suitably be employed.

Other oily vehicles may as well be used provided that they are safe in the volume administered and do not interfere with the therapeutic efficacy of the preparation. As known to the art skilled man, these preparations may also contain anti-microbial agents, to prevent growth of micro-organisms in the preparation, and antioxidants, essentially to prevent the development of rancidity of the oily vehicle.

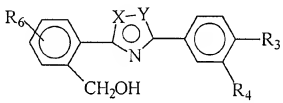
These dosage forms in general contain from 1 to 10% (w/v) of at least one derivative of formula (I) object of the present invention, where the optimum dose/volume ratio depends on the selected dose and the species and size of the animal/subject to be administered.

As an example, the compounds of the present invention can be advantageously prepared starting from a derivative (IX) of the following chemical formula:



(IX)

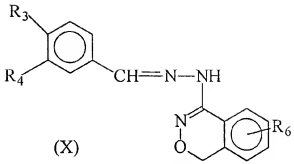
More particularly, when substituents R_1 and R_2 are in position 3 and 5 respectively, the corresponding derivative (XI) has the following chemical formula:



(XI)

The above mentioned derivative of formula (XI), used as starting materials in the process of the present invention, is prepared according to different procedures already reported by the literature. In particular when X=Y=N, the corresponding derivative (XI a) can be advantageously prepared as described in EP11129. In this case the method

This method consists in the rearrangement of hydrazones of substituited benzaldehydes with 4-hydrazino-1H-2,3-benzoxazines of formula (X)



(X)

wherein R_1, R_2 and R_3 are as defined as for the derivatives of formula (I).

This rearrangement simply occurs by refluxing the hydrazone III in a high boiling inert organic solvent, such as for instance, xylene, N,N-dimethylformamide, and halogenated aromatic hydrocarbons, for about 30 minutes and then recovering the compound II by filtration.

Another suitable method for the preparation of the 2-hydroxymethyl-phenyl derivatives of formula (XI a), consists in the oxidation of the corresponding 2-methylphenyl triazoles, either directly to the alcohol (XI a) or to the corresponding carboxylic acid followed by a reduction of this latter to the alcohol(XI a).

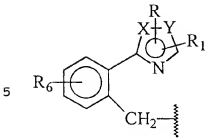
In the former case, ceric ammonium nitrate or silver (II)oxide are the oxidising agents which may be suitably employed, while in the latter, the oxidative step is carried out with any of the several oxidisers known in the art to transform a methyl group on an aromatic ring to a carboxylic group, such as permanganate, nitric acid,

and dichromate, and the reductive step in easily performed with a metal hydride.

Alternatively, the starting compounds of formula II can be prepared by following the process described in EP80053.

Referring to compounds of formula (I), object of the present invention, the procedure for their preparation starting from the corresponding derivative of formula (IX) varies depending whether the substituent R is hydrogen or a group R_8-CO wherein R_8 has the same meaning as above in relation to derivatives of formula (I).

When R is hydrogen, the derivative of formula (IX) is prepared according to different procedures already reported by the literature, in equimolar ratio with phosgene ($COCl_2$) and the resulting chloro-carbonate is left to react with a derivative Z where Z=OR_7 and R_7 is chosen among a saturated or non-saturated, linear or branched aliphatic hydrocarbon C_1-C_{20} , or is chosen according to the following formula:



(XII)

where R, R_1, X and Y are defined as above and R_6 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, or Z is chosen equal to NH-R_8 where R_8 is a linear or branched C_1-C_{20} alkyl chain.

The derivative of formula (I) where R is chosen as hydrogen, can be successively separated from the possible by-products formed during the reaction with phosgene. Phosgene to use is commercially available already dissolved in appropriate solvents.

Following this procedure can be then prepared for example, derivatives (V), (VI) and (VII) of the present invention.

Alternatively, when have to be synthesised derivatives of formula (I) where R_7 is chosen as (XII), asymmetric carbonates, or when R_7 is chosen as saturated or unsaturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, derivative of formula (IX) can undergo

reaction according to the following general scheme, in detail:

⇒ both for the intermediates preparation (alcoholate and imidazolide) and for the end carbonate product, an inert solvent is chosen, i.e. chloroform, dichloromethane, tetrahydrofuran:

⇒ alcoholate preparation is carried out on the selected alcohol using as base NaH or matallic Na either in catalytic or stoichiometric amounts, temperature can be between 0°C and 60°C (optimal room temperature), while reaction time ranges between 30 min to 12 hours (optimal 1 hour);

⇒ the synthesis of the imidazolide of the second alcohol is carried out using as reagent carbonyl-diimidazole with temperature between 0°C and 60°C (optimal, room temperature), while reaction time ranges between 30 min to 12 hours (optimal 1 hour);

⇒ the synthesis of the end carbonates products is carried out by mixing properly the solutions of the alcoholate and of the imidazolide for a time of 6 to 24 hours (optimal 12 hours) at a temperature between 0°C and 60°C (optimal, room temperature).

Merely as an example, not limiting the present invention, a general method for the synthesis of derivatives of formula (I), where R and R_3 are chosen as hydrogens, R_4 is chosen as ethoxyl, R_5 is chosen as $COOR_7$ where R_7 is a linear or branched C1-C20 alkylic chain, is hereafter described:

Example 1

A 50 mL solution of 3-(2-(hydroxymethyl)phenyl)-5-(3-ethoxyphenyl)-1H-1, 2, 4 triazole (3g, 10 mmoles) in tetrahydrofuran, at room temperature, is added an 80% NaH suspension (310 mg, 10 mmoles) in tetrahydrofuran (50 mL). The reaction mixture is shacked at room temperature for 1 hour. The resulting solution is then added to a tetrahydrofuran solution containing the imidazolide of the selected alcohol obtained by reacting the alcoholic derivative (10 mmoles) with 1,1'-carbonyl-diimidazole (1.65 g, 10 mmoles) in tetrahydrofuran (20 mL) for 1 hour at room temperature. The mixture is stirred at room temperature for 12 hours, then solvent is take to dryness under vacuum and the residue re-dissolved in methylene chloride.

The organic phase is washed with water, dried by anhydrous Na_2 SO_4 and evaporated under vacuum. The obtained crude material is purified by column

chromatography on silica gel (eluent hexane-ethylacetate, 8:2, v/v). After evaporation of the solvents, the solid pure product obtained is re-dissolved in hexane, filtered and dried under vacuum.

The compounds described below were prepared according to the procedure reported in Example 1.

Example 2

Preparation of 3-(2-(ethoxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole (XV).

Yield 52%; melting point = 124-126°C

^{1}H-NMR: 7.98 (1H, t, J=4.1 Hz); 7.72-7.74 (6H, m); 7.06 (1H,d, J=6.9 Hz); 5.68 (2H, s); 4.16 (2H, q, J=7.0 Hz), 4.14 (2H, q, J=7.1 Hz); 1.40 (3H, t, J=7.0 Hz); 1.21 (3H, t, J=7.1 Hz).

^{13}C-NMR: 158.76, 154.21, 133.65, 129.83, 129.04, 128.77, 128.60 (2C), 118.16 (2C), 115.86, 112.04 (2C), 67.20, 63.33, 63.15, 14.36, 13.82.

Example 3

Preparation of 3-(2-(butoxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole (XIV).

Yield 58%; melting point= 119-121°C

^{1}H-NMR: 8.00 (1H, t, J=4.8 Hz); 7.70-7.40 (6H, m); 7.03 (1H,d, J=7.2 Hz); 5.62 (2H, s); 4.12 (2H, q, J=7.0 Hz), 4.03 (2H, t, J=6.4 Hz); 1.49 (2H, m); 1.36 (3H, t, J=7.0 Hz); 1.23 (2H, m); 0.80 (3H, t, J=7.3 Hz).

^{13}C-NMR: 158.70, 154.29, 133.51, 129.89, 129.20 (2C), 128.63 (2C), 128.35 (2C), 118.15 (2C), 115.96, 111.98 (2C), 67.27, 67.17, 63.20, 18.03,14.26, 12.98.

Example 4

Preparation of 3-(2-(hexyloxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole (XVI).

Yield 42%; melting point = 90-92°C

^{1}H-NMR: 8.07 (1H, m); 7.69-7.40 (6H, m); 7.06 (1H, d, J=7.3 Hz); 5.68 (2H, s); 4.15 (2H, q, J=7.0 Hz), 4.07 (2H, t, J=6.6 Hz); 1.56 (2H, m); 1.40 (3H, t, J=7.0 Hz); 1.23 (6H, m); 0.85 (3H, t, J=6.5 Hz).

^{13}C-NMR: 158.76, 154.29, 133.65, 129.79, 128.87 (2C), 128.59 (2C), 128.15 (2C), 118.15 (2C), 115.87, 112.03 (2C), 67.37, 67.29, 63.13, 30.49, 27.87, 24.52, 21.61,14.36, 13.43.

Example 5

Preparation of 3-(2-(octyloxy-carbonyloxymethyl)phenyl-5-(3-ethoxyphenyl)-1H-1, 2, 4-triazole (XVI).

Yield 49%; melting point= 86-89°C

^{1}H-NMR: 8.06 (1H, m); 7.72-7.40 (6H, m7); 7.05 (1H, d, J=7.1 Hz); 5.69 (2H, s); 4.15 (2H, q, J=7.0 Hz), 4.07 (2H, t, J=6.4 Hz); 1.56 (2H, m); 1.40 (3H, t, J=7.0 Hz); 1.23 (10H, m); 0.86 (3H, t, J=6.5 Hz).

^{13}C-NMR: 158.76, 154.28, 133.65, 129.77, 129.01, 128.84, 128.59 (2C), 128.59 (2C), 128.13 (2C), 118.16 (2C), 115.83, 112.03 (2C), 67.37, 67.30, 63.13, 30.88, 27.91, 24.89, 21.72,14.35, 13.53.

In the following example 6, the synthesis of one derivative of formula (I), where the group R_7 is chosen of formula (XII), symmetric carbonates, is described:

Example 6

Preparation of Di-(2-(5-(3-ethoxyphenyl)-1H-1, 2, 4-triazol-3-yl) phenylmethyl) carbonate (XVII).

A 15 mL solution of 3-(2-(hydroxymethyl)phenyl)-5-(3-ethoxyphenyl)-1H-1, 2, 4 triazole (0.7g, 2.4 mmoles) in tetrahydrofuran, at room temperature, is added a 80% NaH suspension (35 mg, 1.2 mmoles) in tetrahydrofuran (15 mL). The reaction mixture is shacked at room temperature for 1 hour. The resulting solution is then added 1,1'-carbonyl-diimidazole (192 mg, 1.2 mmoles) in tetrahydrofuran (20 mL) for 1 hour at room temperature. The mixture is stirred at room temperature for 12 hours. Solvent is taken to dryness under vacuum and the residue

re-dissolved in methylene chloride. The organic phase is washed with water, dried by anhydrous Na_2 SO_4 and evaporated under vacuum. The obtained crude material is purified by column chromatography on silica gel (eluent hexane-ethylacetate, 7:3, v/v). After evaporation of the solvents, the solid pure product obtained is re-dissolved in hexane, filtered and dried under vacuum. 212 mg of the compound (XVII) are obtained.

Yield 36%; melting point = 143-145°C

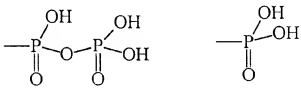
^{1}H-NMR: 8.07 (2H, m), 7.69-7.38 (12H, m); 7.03 (2H,d, J=8.4 Hz); 5.72 (4H, s); 4.12 (4H, q, J=7.0 Hz), 1.37 (6H, t, J=7.0 Hz);.

^{13}C-NMR: 158.74, 154.21, 133.59, 129.81 (2C), 128.97 (2C), 128.02 (2C), 118.18 (2C), 115.88, 112.00 (2C), 67.41, 63.13, 14.33.

When R is chosen equal to -CO R_8, where R_8 is a saturated or a non saturated C_1- C_{10} aliphatic hydrocarbon, the hydroxy group of derivative (IX), will be protected according to known methods. Protected derivative (IXb) will be also obtained and acylated according to known methods in order to introduce the -COR_8 group. Subsequently these acylated derivatives will be de-protected and allowed to react with phosgene as

reported above. In the case of X=Y=N, the acylation reaction could be carried out as described by EP80053.

When R_5 is chosen:



Derivatives of formula (I) are advantageously prepared starting from derivatives of formula (IX) (eventually submitted to a previous acylation reaction as already described) by reaction with phosphoric acid or equivalents according to known methods. For example, following this procedure derivative (VIII), object of the present invention, is prepared..

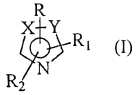
For derivatives of formula (I), when X=Y=N and R=H, following the acylation procedure described above, both single compounds, where the substituent R is located on one of the two adjacent nitrogen atoms and mixtures of the two possible isomers can be obtained.

In this latter case, being established that each isomer retains the same anti-gestative immuno-suppressant and anti tumour activity, the mixture can be separated into the single components by chemico-physical known methods. For example, the way a mixture can be resolved into the single components is a fractionated crystallisation,

which take advantage of the different solubility of each compound in various solvents at different temperatures. Suitable solvents that can be used for this method are chosen as an example, among hexane, ethyl-acetate, C_1-C_4 alkyl ethers, methylen chloride, light petroleum ether and mixtures thereof. A further illustrative example of a method useful for the separation of the isomers' mixture is based on column chromatography, performed on non-acid, buffered adsorbents, as silica-gel buffered to ph=7. Another example of a method useful for the separation of the isomer mixture is based on the use of preparative high pressure liquid chromatography (PHPLC), carried out on proper columns, for example filled with silica-gel esterified with octyl-silane or octyl-decylsilane. Other obvious procedures useful for resolving a mixture of isomers into the single components are intended to fall within the scopes of the invention.

CLAIMS

1. Nitrogen heterocyclic aromatic derivatives having the following general formula:



(I)

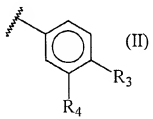
where:

-when X=Y, X, Y=N;

-when X=Y, X, Y=N, C, CH;

-R is chosen between hydrogen, $-COR_8$ where R_8 is a saturated or non-saturated aliphatic hydrocarbon C_1-C_{10}, or R represents any other group able to form a bond with a nitrogen atom;

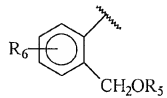
- R_1 has the following general formula:



(II)

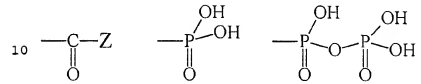
where R_3 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, R_4 is chosen among hydrogen, alkyl or alkoxyl C_1-C_{10}, or R_3 and R_4 together form a methylendioxy group;

- R_2 has the following general structure:

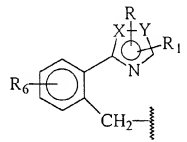


(III)

where R_5 is chosen among:



where Z=OR_7 with R_7 is chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, or is chosen according to the following formula:



(XII)

where R, R_1, X and Y are defined as above and R_6 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, or Z is chosen equal to NHR_8 where R_8 is a linear or branched C_1-C_{20} alkyl chain. Mentioned R_1 and R_2 are never

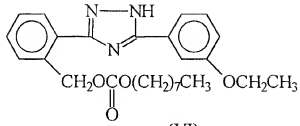
located on two adjacent atoms of the heterocyclic aromatic ring.

2.Nitrogen heterocyclic aromatic derivatives according to the claim 1. characterised by a saturated or non-saturated C1- C_{20} aliphatic hydrocarbon represented by a linear or branched alkyl, alkenyl or alkinyl which can contain one or more double or triple bonds. Always according to the present invention, the term alkyl or alkoxyl means a linear or branched C_1-C_{10} alkyl or alkoxyl group.

3.Nitrogen heterocyclic aromatic derivatives according to the claim 1. characterised by the fact that are derivatives of pyrazole, imidazole and 1H-1, 2, 4-triazole respectively:

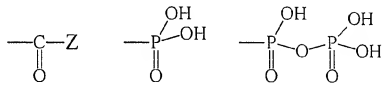


4.Nitrogen heterocyclic aromatic derivatives according to the claim 1, characterised by having X=Y=N, R=H and showing the following general formula:

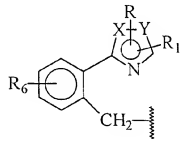


(VI)

where R_3 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, R_4 is chosen among hydrogen, alkyl or alkoxyl C_1-C_{10}, or R_3 and R_4 together form a methylendioxy group, where R_5 is chosen among:



where Z=OR_7 with R_7 is chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, or is chosen according to the following formula:



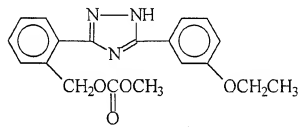
(XII)

where R, R_1, X and Y are defined as above and R_6 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10},

or Z is chosen equal to NHR_8 where R_8 is a linear or branched C_1-C_{20} alkyl chain.

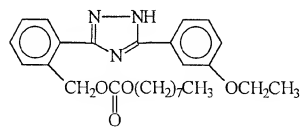
5. Nitrogen heterocyclic aromatic derivatives according to claim 4. characterised by having R_6 = hydrogen, R_4 = OCH_3 or OCH_2CH_3. Mentioned R_3 is hydrogen, mentioned R_5 is chosen equal to COZ where Z=OR_7 with R_7 as a saturated linear aliphatic C_1-C_{12} hydrocarbon.

6. Nitrogen heterocyclic aromatic derivative according to claim 1. having the following chemical structure:



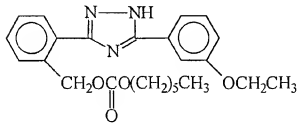
(V)

7. Nitrogen heterocyclic aromatic derivative according to claim 1. having the following chemical structure:



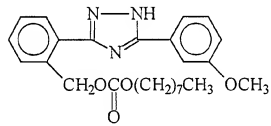
(VI)

8.Nitrogen heterocyclic aromatic derivative according to claim 1. having the following chemical structure:



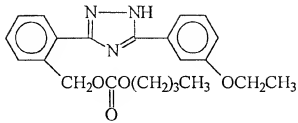
(XVI)

9. Nitrogen heterocyclic aromatic derivative according to claim 1.having the following chemical structure:



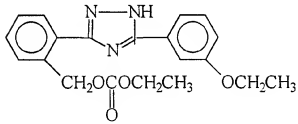
(XIII)

10.Nitrogen heterocyclic aromatic derivative according to claim 1. having the following chemical structure:



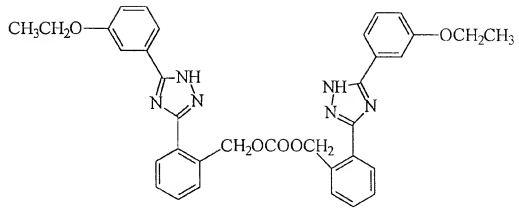
(XIV)

11.Nitrogen heterocyclic aromatic derivative according to claim 1. having the following chemical structure:



(XV)

12.Nitrogen heterocyclic aromatic derivative according to claim 1.having the following chemical structure:



(XVII)

13.Use of the nitrogen heterocyclic aromatic derivatives, according to claim 1., as anti-gestative agents.

14.Use of the nitrogen heterocyclic aromatic derivatives, according to claim 1, as immuno-suppressant agents.

15. Use of the nitrogen heterocyclic aromatic derivatives, according to claim 1., for the preparation of a drug with anti-gestative activity.

16.Use of the nitrogen heterocyclic aromatic derivatives, according to claim 1., for the preparation of a drug with immuno-suppressant activity.

17. Pharmaceutical composition with anti-gestative action which contains at least one nitrogen heterocyclic aromatic derivative, according to claim 1., as active principle.

18. Pharmaceutical composition with immuno-suppressant action which contains at least one nitrogen heterocyclic aromatic derivative, according to claim 1., as active principle.

19. Pharmaceutical composition according to claims 17 and 18., formulated utilising systems suitable for a transdermic release.

20. Pharmaceutical composition according to claims 17 and 18., formulated utilising proper aqueous systems suitable for an intravenous administration.

21. Pharmaceutical composition according to claim 17 and 18., formulated utilising vegetable oils or esters of fatty acids, i.e, sesame oil, suitable for an epicutaneous, subcutaneous and intramuscular administration.

22. Pharmaceutical composition according to claim 21., formulated utilising oils of vegetable origin or fatty esters such as sesame oil, corn oil, peanut oil, cotton seed oil, and ethyl oleate.

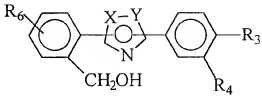
23. Pharmaceutical composition according to claim 17 and 22., formulated utilising previously disclosed anti-microbic agents

24. Pharmaceutical composition according to claim 17 and 22., formulated utilising previously disclosed anti-oxidative agents.

25. Pharmaceutical composition according to claim 17 and 24., containing from 1 to 10 % (w/v) of at least one nitrogen heterocyclic aromatic derivative according to claim 1.

26. Method of preparation of nitrogen heterocyclic aromatic derivative according to claim 1, which involves the following synthesis phases:

a) preparation of one nitrogen heterocyclic aromatic derivative of general formula

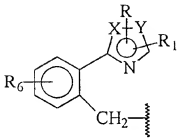


(IX)

b) possible protection of the OH group, possible acylation reaction with introduction of a $-COR_8$ group leading to the formation of an acylated derivative, subsequent de-protection of the OH group, and alternatively:

c) reaction of derivative (IX) with a carbonatante agent, to give rise to a corresponding carbonate product.

d) reaction of the above mentioned carbonate with Z to obtain the mentioned derivative (I). Where $Z=OR_7$ with R_7 is chosen among a saturated or non-saturated, linear or branched C_1-C_{20} aliphatic hydrocarbon, or is chosen according to the following formula:



(XII)

where R, R_1, X and Y are defined as above and R_6 is chosen among hydrogen, halogen, alkyl or alkoxyl C_1-C_{10}, or Z is chosen equal to NHR_8 where R_8 is a linear or branched C_1-C_{20} alkyl chain;

or: reaction of the above mentioned derivative (IX) with phosphoric acid or equivalent products, with formation of the derivative of formula (I).

27. Procedure according to claim 26, characterised by selecting as carbonatante agent phosgene ($COCl_2$).

INTERNATIONAL SEARCH REPORT

Int. dional Application No
PCT/EP 98/03496

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D249/08 C07D233/64 C07D231/12 C07F9/6518 C07F9/6503
A61K31/41 A61K31/675

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 440 364 A (GRUPPO LEPETIT S.P.A.) 30 May 1980 cited in the application see the whole document, particularly page 31, lines 19, 20 and 28, and page 32, lines 14, 15 and 19 ---	1-27
X	EP 0 080 053 A (GRUPPO LEPETIT S.P.A.) 1 June 1983 cited in the application see the whole document ---	1-27
A	US 4 119 635 A (OMODEI-SALÈ A ET AL) 10 October 1978 see the whole document, particularly examples 19-24 ---	1-27
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 1998	14/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

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Form PCT/ISA/210 (second sheet) (July 1992)

3/26/2008, EAST Version: 2.2.1.0

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	TOJA E ET AL: "Synthesis and pregnancy terminating activity of 2-aryl pyrazolo'5,1-a!isoindoles and isoquinolines" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY - CHIMICA THERAPEUTICA, vol. 17, no. 3, 1982, pages 223-7, XP002078326 Paris, FR see the whole document, particularly comound 26 -----	1-27

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/03496

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13 and 14
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 13 and 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

3/26/2008, EAST Version: 2.2.1.0

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intl. .ional Application No
PCT/EP 98/03496

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ..tional Application No
PCT/EP 98/03496

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